

REACTIONS OF AMINES
WITH POLYHYDROXYCARBONYL COMPOUNDS

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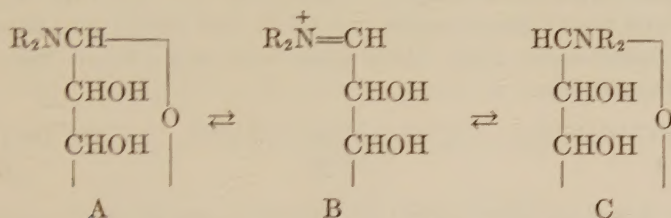
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THE REARRANGEMENT OF THE 3-C-PHENYLTRIOSES

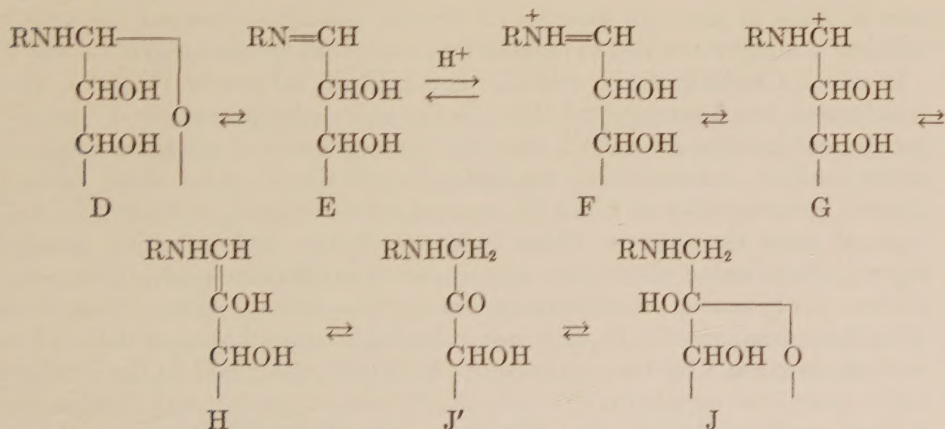
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When primary or secondary amines react with aldopentoses or aldohexoses, the initial products are glycosylamines. Certain of these glycosylamines—those derived from primary amines and from secondary *aliphatic* amines—undergo mutarotation in solution, probably *via* a Schiff base or the cation of a Schiff base ($A \rightarrow B \rightarrow C$).



Glycosylamines derived from secondary *aromatic* amines do not undergo mutarotation, and it has been suggested (1) that the reason for this lies in the very weak basicity of the nitrogen atom in these compounds—*i.e.*, cation B is not formed. All glycosylamines are unstable toward acids (1-4), although the stability in water varies widely. Moreover, glycosylamines derived from *primary*, *aromatic* amines (D)—and only these—will undergo Amadori rearrangement to isoaminoglycosides (J) (5). Weygand (5) has suggested that this rearrangement involves stages D to J inclusive.



The trioses glyceraldehyde and dihydroxyacetone, under certain conditions, rearrange to methylglyoxal with loss of the elements of water (6). In dilute acetic

¹ Abstracted from a thesis by Ray H. Anderson, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1950.

acid, glyceraldehyde is converted into methylglyoxal only in the presence of a *primary aromatic* amine, whereas dihydroxyacetone in the same solvent forms the ketoaldehyde whether or not an amine is present. Thus there is a certain similarity between the conditions for this transformation of glyceraldehyde and those required for the Amadori rearrangement.

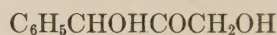
Because of the complexity of the reactions which may occur between aqueous solutions of simple sugars and amines, it appeared worthwhile to investigate this reaction for some simple isomeric sugars in which one of the carbon atoms was marked, and in which the reactions would not be complicated by the opening and closing of furanose or pyranose rings. Chosen for this purpose were the three 3-C-phenyltrioses: β -phenylglyceraldehyde (I), α,β -dihydroxypropionophenone (II), and phenyldihydroxyacetone (III). The behavior of these three substances, in dilute acetic acid, was studied with and without the inclusion of amines in the solution.



I



II

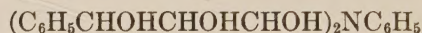


III

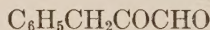
Reaction of β -phenylglyceraldehyde (I) with excess aniline in aqueous solution led to an oily, yellow Schiff base (IV) which was unstable at room temperature. When I was present in excess, a white, solid bis-compound V was formed. The primary products IV and V



IV



V



VI

were insoluble in water. In studying the further transformations of I, IV, and V, sufficient dioxane was added to the solutions to prevent precipitation of IV and V.

In solution in dilute acetic acid and dioxane, both substances IV and V were transformed into benzylglyoxal (VI). In the same solvent mixture, I was also transformed into the glyoxal VI, but only in the presence of a primary aromatic amine (aniline, *m*-nitroaniline, *p*-toluidine, *o*-toluidine): under these circumstances, transformation of I into VI occurred to the extent of at least 66% in 72 hours at room temperature. Other types of amines—diphenylamine, methyl-aniline, ethanolamine, ethylamine, amylamine, phenylalanine ester, glycine ester, glycine, diethylamine, *n*-ethylethanolamine—were without effect. Presence of VI in these solutions of I, IV, or V was indicated by precipitation of the *m*-nitrobenzoylosazone of VI when *m*-nitrobenzoylhydrazide was added to the solutions but in order to be certain that VI was actually present, a solution of I and aniline in dilute acetic acid was distilled with steam. Benzylglyoxal VI was isolated from the distillate and identified by comparison with an authentic specimen of VI.

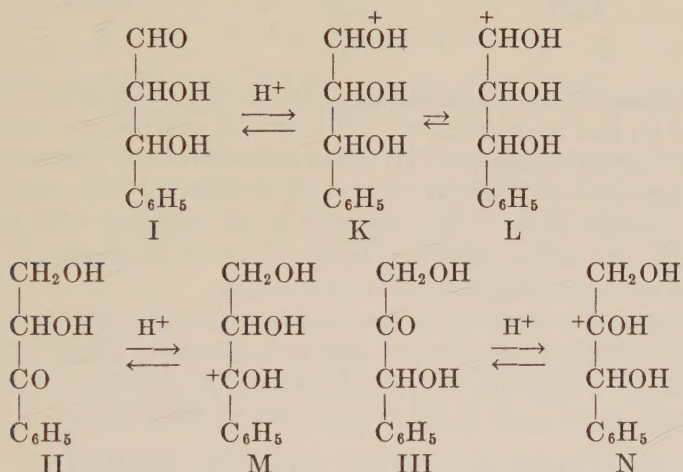
Both of the ketotrioses II and III were transformed, in dilute acetic acid, into acetylbenzoyl (VII) with loss of the elements of water.



VII

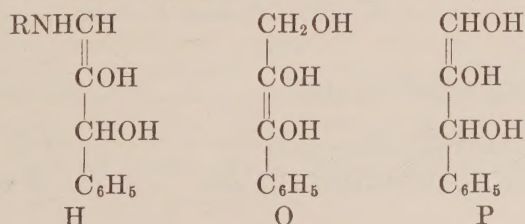
Although the transformations of II and III took place at a rate of only about 25% of that of I, the transformations of II and III occurred even if no amine were present in the solution. The only change brought about by addition of aniline to solutions of II and III in dilute acetic acid was a slight increase in the rate of the transformation of these substances into VII.

These data concerning the rearrangement of the phenyltrioses can be interpreted quite well on the basis of Weygand's outline of the Amadori rearrangement (5). The key intermediate is a cation such as G; unless this is formed, the reaction will stop at stage F. This fact gives a possible explanation for the requirement of the presence of a primary aromatic amine in order that the aldatriose may rearrange, whereas it is not a necessary requirement for the rearrangement of a ketotriose. Thus, the equilibrium for the aldose (I, K, L) is unfavorable to the formation of the secondary cation L, but in the case of the ketoses, the equilibria, leading respectively to the tertiary cations M and N are more favorable.

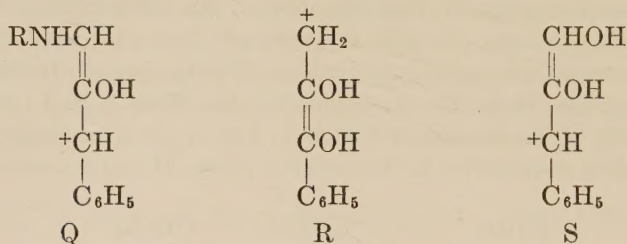


In the case of aldoses, the presence of an amine results in the formation of E and then F, and so to a favorable equilibrium as far as F, but G cannot form unless the charge can be transferred from the nitrogen to the carbon ($\text{F} \rightarrow \text{G}$) to a sufficient degree that the subsequent steps of the reaction may occur. This means that the amine must be one giving a Schiff base (E) of just the proper basicity so that the change $\text{F} \rightarrow \text{G}$ may occur, and it has been found that a primary aromatic amine satisfies these requirements.

The next step, in all cases, appears to be the expulsion of a proton, resulting in the formation of H from G, O from M, and O and/or (unlikely) P from N.



In those cases (pentoses, hexoses) in which a tautomeric shift of H may lead to a compound capable of undergoing ring closure to a furanose or pyranose form, these changes may occur ($H \rightarrow J' \rightarrow J$) and Amadori rearrangement results. It may be that the ability of J' to undergo ring closure is the determining factor in whether or not Amadori rearrangement occurs, but this cannot be said with certainty. In any event, if the change $H \rightarrow J' \rightarrow J$ does not occur, the next step appears to be elimination of the β (allylic?) hydroxyl group (5, 7) producing new cations Q, R, S ($= Q$) from H, O, and P respectively.



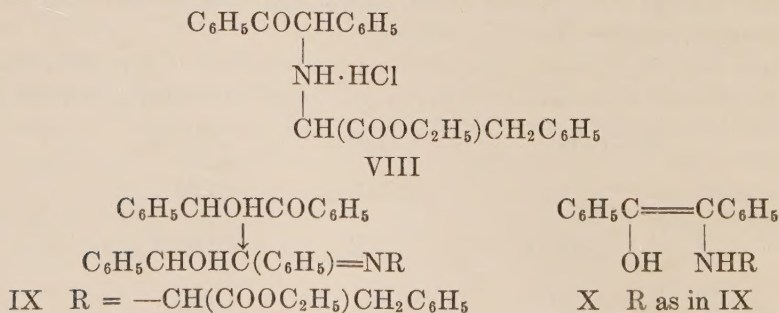
These new cations, by tautomeric shifts and expulsion of a proton (also hydrolysis in the case of Q) lead to benzylglyoxal (VI) from Q and S and to acetylbenzoyl VII from R. That acetylbenzoyl (VII) was produced from both ketoses II and III shows that expulsion of a proton from cation N (derived from III), though it might have occurred in two ways, occurred in one way only—the proton was eliminated from the carbon atom next to the phenyl group leading to O, R, and then VII and not to benzylglyoxal (VI) *via* P and S.

As a preliminary to this study of the reactions of the phenyltrioses, the reaction between a simple ketol, benzoin, and an amino ester, phenylalanine ethyl ester, was studied. Previously, condensation of benzoin had been reported in the case of aromatic amines only (8, 9); in every case an aminoketone was produced



Recently Lutz, Freek, and Murphy (10) reported the formation of aminoketones from benzoin and aliphatic amines when phosphorus pentoxide was used as the condensing agent.

By use of a modification of the procedure of Lutz, *et al.*, a stable, crystalline hydrochloride VIII was obtained from benzoin and phenylalanine ethyl ester.



The hydrochloride melted at 174–176°, and from it the crystalline base, melting at 104–105°, was obtained. This base was stable at 0°, but was unstable when kept at room temperature.

The formation of this condensation product may be regarded as occurring *via* the mechanism discussed above for the reaction between hydroxycarbonyl compounds and amines. The initial step involves formation of the Schiff base IX (corresponding to E); this leads to the cations corresponding to F and G. A proton is expelled from the latter, leading to the enol X which then undergoes a tautomeric shift, forming VIII. It should be noted that, if this mechanism is correct, the carbonyl group in the product VIII is not the one present originally in the benzoin molecule, for this mechanism leads to a compound in which the original carbonyl group has been “reduced” whereas the alcohol group has been “oxidized”, *i.e.*, a sort of Amadori rearrangement. This point, however, was not examined experimentally.

EXPERIMENTAL PART²

Cinnamaldehyde diethyl acetal (96.5 g., 81%) was prepared from cinnamaldehyde (66 g.) and ethyl orthoformate (82 g.) in ethanol (87 g.) as described by Claisen (11). The product boiled at 120–123°/3 mm., n_D^{25} 1.5121.

β-Phenylglyceraldehyde diethyl acetal. It was not possible to duplicate the preparation of this substance from cinnamaldehyde acetal as described by Fischer and Hoffa (12). Invariably *black* manganese hydroxide separated, and no hydroxylation occurred (13). Hydroxylation was successful, however, when the method of Rüber was used (14). A solution of cinnamaldehyde acetal (25.4 g.) in ethanol (1.5 l.) was cooled to –40° and held at that temperature and stirred vigorously while a solution of potassium permanganate (24 g.) in water (800 cc.) was slowly (4 hours) added. The mixture was allowed to attain room temperature and the *brown* manganese dioxide was removed. The filtrate, after concentration under reduced pressure to a volume of 200 cc., was extracted with four 100-cc. portions of ether. The combined extracts were dried and the solvent was removed. The residual yellow oil (16 g., soluble in ether and ethanol, sparingly soluble in petroleum ether) was dissolved in boiling petroleum ether (3 l.), and the solution was cooled (0°). After one hour, an oil (6 cc.) separated; the supernatant liquid was decanted and again cooled (0°). The oil was dissolved in boiling petroleum ether (1 l.) and this solution was cooled (0°). Both solutions deposited crystalline material after about an hour. The solid was removed from the combined solutions and recrystallized from petroleum ether. It then weighed 6 g. (13%) and melted at 38°. In another experiment, double quantities of materials were used; in this case, the product weighed 20 g., (21%) and melted at 38°.

Anal. Calc'd for $C_{13}H_{20}O_4$: C, 65.06; H, 8.33.

Found: C, 64.80; H, 8.21.

β-Phenylglyceraldehyde (I). The above acetal (5 g.) was stirred rapidly with aqueous sulfuric acid (50 cc., 0.5%) until the mixture became homogeneous. Excess barium carbonate was added, the mixture was filtered and the filtrate was set aside at room temperature. After several hours, the solid was removed, washed with cold water, crystallized from a mixture of dioxane and petroleum ether, and dried at 85° under reduced pressure for two days. It then weighed 2.5 g. (70%), sintered at 118°, and melted at 123–125°. The melting point and the composition of this material depended upon the length of time, etc., it was dried; it was not possible to obtain it in anhydrous form. These properties were observed previously by Fischer and Hoffa (12). The substance reduced Fehling's solution, and Tol-

² Microanalyses by R. W. Amidon, Jay S. Buckley, William Cummings, R. E. Kelly, and H. W. Turner.

lens' reagent at room temperature and it formed a phenylhydrazone which, after crystallization from ethanol, melted at 167–168° [reported m.p. 170° (12)]. The substance gave poor analytical values, as observed by Fischer and Hoffa (12).

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.06; H, 6.03.

Found: C, 63.64; H, 6.62.

Schiff base (IV). A cold solution of I (0.5 g.) in water (20 cc.) was added, slowly and with stirring, to a cold solution of excess (200%) aniline (1 g., distilled from zinc dust) in water (20 cc.) containing acetic acid (1 cc.). A yellow oil separated immediately; this was removed, washed with water, taken up in ether, and the ethereal solution was dried. Removal of the solvent left IV as a yellow oil (0.45 g., 65%).

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.70; H, 6.06; N, 5.81.

Found: C, 74.56; H, 6.82; N, 6.04.

This material was not stable; after several days at room temperature, it became dark and viscous; satisfactory analytical values were difficult to obtain. It reduced Fehling's solution, Tollens' solution, and an alkaline solution of methylene blue at room temperature. Action of dilute (5%) hydrochloric acid upon IV resulted in immediate production of aniline.

Bis-compound (V). A cold solution of aniline (0.3 g., 0.003 mole) in water (20 cc.) containing acetic acid (1 cc.) was added, slowly and with stirring, to a cold (0°) solution of I (0.5 g., 0.003 mole) in water (20 cc.). After 15 minutes, the white solid was removed and washed with cold water. The product was dried under reduced pressure at room temperature, when it weighed 0.4 g. (60%), m.p. 59–64°. It decomposed at temperatures above about 20°; it could not be recrystallized, for warm solutions of it in alcohol or dioxane either with or without a little acetic acid, deposited a brown tar in a short time.

Anal. Calc'd for $C_{24}H_{27}NO_6$: C, 67.76; H, 6.40; N, 3.30.

Found: C, 67.82; H, 6.97; N, 3.16.

Benzylglyoxal (VI) (2.3 g., 6%) was prepared from benzyl chloride (31 g.) as described by Dakin (15). The *p*-nitrophenylosazone melted at 276–280°; Dakin reported m.p. 275–280°. When VI (0.2 g.) in acetic acid (1 cc.) and dioxane (5 cc.) was added to a solution of *m*-nitrobenzhydrazide (0.5 g.) in dioxane (5 cc.) and water (10 cc.), the solution, after standing for three days, deposited the *m*-nitrobenzoylosazone of VI. This material, after crystallization from hot dioxane, weighed 0.34 g. (57%), m.p. 190–192°.

Anal. Calc'd for $C_{22}H_{18}N_6O_6$: C, 58.22; H, 3.80; N, 17.72.

Found: C, 58.14; H, 3.88; N, 17.60.

Rearrangement of IV and V. The Schiff base IV (0.2 g.) in purified (16) dioxane (1 cc.) was added to a solution of *m*-nitrobenzhydrazide (0.4 g.) in acetic acid (1 cc.), water (5 cc.), and dioxane (4 cc.). After three days at room temperature, the solid was crystallized from dioxane and dried at 100° under reduced pressure. It weighed 0.18 g. (45%), and melted at 187–189° alone or when mixed with the *m*-nitrobenzoylosazone of VI. In a duplicate experiment, but using V (0.2 g.), the product weighed 0.15 g. (32%) and melted at 187–189°, alone or when mixed with the product from IV.

Rearrangement of I. A solution of I (0.5 g.), aniline (1 g.), and *m*-nitrobenzhydrazide (2 g.) in dioxane (10 cc.) and acetic acid (1 cc.) deposited no precipitate after three days at room temperature. Addition of water (10 cc.) brought about deposition of solid within three days; this material (0.97 g., 66%) melted at 188–190° alone or when mixed with the product from either IV or V.

Anal. Calc'd for $C_{22}H_{18}N_6O_6$: C, 58.22; H, 3.80; N, 17.72.

Found: C, 58.39; H, 4.02; N, 17.59.

This experiment was repeated with changes and results as follows: Omission of either aniline or acetic acid resulted in no deposition of solid after six days; substitution of *p*-toluidine, *o*-toluidine, or *m*-nitroaniline for aniline led in each case to the *m*-nitrobenzoylosazone of VI as shown by mixture melting point; substitution of aniline by diphenylamine, methylaniline, ethanolaniline, ethylamine, amylamine, phenylalanine ethyl ester, glycine ethyl ester, glycine, diethylamine, or *N*-ethylethanolamine led in each case to no deposition of solid after six days.

A solution of I (0.3 g.) in water (20 cc.) was added dropwise (20 minutes) and with stirring to a solution of aniline (0.4 g.) in water (5 cc.) containing acetic acid (0.5 cc.). The temperature was maintained at 5° during addition, and the solution was maintained at 0° for one hour afterward. The solution was extracted twice with 25-cc. portions of ether, the combined extracts were dried, and the solvent was removed under reduced pressure at room temperature. The residual yellow oil was stirred into cold water (50 cc.) containing acetic acid (1 cc.) and the mixture was distilled with steam until the oil became a brown tar. About 0.04 g. of white crystalline material collected in the condenser; this melted at 119–121° alone or when mixed with VI.

Anal. Calc'd for $C_9H_8O_2$: C, 72.97; H, 5.41.

Found: C, 72.96; H, 5.58.

This material gave a *p*-nitrophenylosazone melting at 273–277°, as reported by Dakin (15).

β-Chloropropiophenone (24 g., 60%) was prepared from benzene and *β*-chloropropionyl chloride (30 g.), as described by Hale and Britton (17).

Vinyl phenyl ketone (18). *β*-Chloropropiophenone (12 g.) was added to a hot solution of potassium acetate (6 g., freshly fused) in ethanol (100 cc.). The mixture was cooled to room temperature and was filtered. The filtrate, containing the vinyl phenyl ketone (theoretical yield, 9 g.) was used immediately for the next step.

α,β-Dihydroxypropio-phenone (II). The above filtrate was diluted to 700 cc. with ethanol, cooled to –40°, and potassium permanganate (12 g.) in water (400 cc.) was added slowly (four hours) with vigorous stirring. The mixture was allowed to come to room temperature, the brown manganese dioxide was removed, and the filtrate, concentrated to 100 cc. under reduced pressure, was extracted with four 50-cc. portions of ether. The combined extracts were dried, concentrated to 20 cc., diluted with petroleum ether (10 cc.), and placed in a refrigerator at 0° for a day. The solid was crystallized from a mixture of ether and petroleum ether. It weighed 2.8 g. (25%) and melted at 80°. It reduced Fehling's solution, and an alkaline solution of methylene blue at room temperature.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.06; H, 6.03.

Found: C, 65.27; H, 6.35.

The *p*-nitrophenylhydrazone, crystallized from aqueous ethanol, was orange-brown, m.p. 171–173°.

Anal. Calc'd for $C_{16}H_{15}N_3O_4$: C, 59.80; H, 4.98; N, 13.95.

Found: C, 60.08; H, 5.26; N, 13.81.

Acetylbenzoyl (VII) (14 g., 62%) was prepared from isonitrosopropiophenone (25 g.) as described by Hartman and Roll (19).

The *m*-nitrobenzoylosazone, prepared from VII (0.2 g.) and *m*-nitrobenzhydrazide (0.5 g.) in aqueous dioxane containing acetic acid, weighed 0.3 g. (50%). After crystallization from ethanol, the substance melted at 186–187°.

Anal. Calc'd for $C_{23}H_{18}N_6O_6$: C, 58.22; H, 3.80; N, 17.72.

Found: C, 58.33; H, 3.92; N, 17.56.

Acetylmandeloyl chloride (20 g., 69%) was prepared from mandelic acid (21 g.) as described by Thayer (20).

Acetylmandeloyldiazomethane. Acetylmandeloyl chloride (6 g.) in ether (20 cc.) was added, dropwise and with stirring, to a cold (0–5°) solution of diazomethane [from 12 g. of nitrosomethylurea (21)] in ether (170 cc.). The mixture was allowed to stand at room temperature for four hours, then was concentrated to a volume of 20 cc., and kept at 0° for four hours. The solid diazoketone was removed, washed with cold ether, and crystallized from a mixture of dioxane and petroleum ether. The slightly yellow product weighed 3.2 g. (60%), m.p. 48–50°. It decomposed on standing in a vacuum desiccator for three days at room temperature, and was not analyzed.

Phenyldihydroxyacetone diacetate. A solution of the diazoketone (2 g.) in acetic acid (25 cc.) containing a trace of cupric acetate (40 mg.) was heated to the boiling point (22). After the evolution of gas subsided, the solution was concentrated under reduced pressure at 50° to a volume of 5 cc. and then diluted with chloroform (40 cc.). This solution was washed three times with water, dried, and evaporated under reduced pressure. The residual

sirup was dissolved in acetic anhydride (25 cc.) containing zinc chloride (0.3 g.); the solution was allowed to stand overnight and was then poured into ice-water (100 cc.). The mixture was extracted with ether, the extract was dried, and the solvent was evaporated. The semi-solid residue was recrystallized from a mixture of dioxane and petroleum ether. The diacetate weighed 0.5 g. (25%), m.p. 39–41°.

Anal. Calc'd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.65.

Found: C, 62.56; H, 5.48.

Phenyldihydroxyacetone (III). A cold (0°) solution of barium hydroxide octahydrate (2 g.) in water (10 cc.) was added, with rapid stirring, to a cold (0°) solution of the above diacetate (0.5 g.) in water (10 cc.) and ethanol (10 cc.). The mixture was stirred at 0° for two hours, and was then saturated with carbon dioxide. The solid was removed, and the filtrate, when allowed to stand in an open beaker at room temperature for two days, deposited a crystalline solid. This was crystallized from aqueous ethanol; weight, 0.21 g. (60%); m.p. 71–73°, reduces Fehling's solution or an alkaline solution of methylene blue at room temperature. A mixture of III with II (m.p. 80°) melted at 66–70°.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.06; H, 6.03.

Found: C, 65.06; H, 6.22.

The *p*-nitrophenylhydrazone, crystallized from aqueous ethanol, melted at 162–164°. A mixture of this with the *p*-nitrophenylhydrazone of II (m.p., 171–173°), melted at 154–159°.

Anal. Calc'd for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 4.98; N, 13.95.

Found: C, 59.94; H, 4.81; N, 13.81.

Rearrangement of II. Water (2 cc.) was added to a solution of II (0.1 g.) and *m*-nitrobenzhydrazide (0.4 g.) in dioxane (2 cc.) containing acetic acid (0.2 cc.), and the mixture was allowed to stand at room temperature. After three days, 0.05 g. of solid had separated; after ten days, no further solid separated, and the total amount of solid was 0.14 g. The experiment was duplicated except that aniline (0.2 g.) was added to the solution. After three days the solid weighed 0.07 g., and after ten days the total precipitate weighed 0.17 g. The solids from these experiments melted at 183–186°, alone or when mixed. After crystallization from dioxane, the material melted at 185–187°, alone or when mixed with the *m*-nitrobenzoylosazone of acetylbenzoyl (VII). The solid from either experiment, when mixed with the *m*-nitrobenzoylosazone (m.p. 190–192°) of benzylglyoxal (VI) melted at 178–184°.

Rearrangement of III. The experiments reported for the rearrangement of II were duplicated exactly, substituting III for II. In the experiment in which no aniline was added, the precipitates after three and ten days weighed 0.04 g. and 0.13 g., respectively. In the experiment in which aniline was added, the precipitates after three and ten days weighed 0.06 g. and 0.15 g., respectively. These solids melted at 174–178°, alone or when mixed. After crystallization twice from a mixture of nitrobenzene and toluene, the solids melted at 184–186°, alone or when mixed with each other or with the *m*-nitrobenzoylosazone (m.p. 186–187°) of acetylbenzoyl (VII). When mixed with the *m*-nitrobenzoylosazone (m.p. 190–192°) of benzylglyoxal (VI) either solid melted at 175–180°.

Phenylalanine ethyl ester (6.8 g., 58%) was prepared from DL-phenylalanine (10 g.) as described by Fischer (23).

Reaction of benzoin with phenylalanine ethyl ester. Benzoin (2.3 g.), the ester (2.3 g.), and phosphorus pentoxide (0.15 g.) were mixed and the mixture was heated for one hour under reduced pressure (10). The mixture was cooled, stirred with dry ether (20 cc.), the ether solution was decanted, and to it was added, with rapid stirring, a solution of hydrogen chloride in ether (10 cc., 12%). The white, granular hydrochloride (2.5 g., 50%) was crystallized twice from a mixture of ethanol and ether; weight, 1.5 g.; m.p. 167–169°.

Anal. Calc'd for $C_{25}H_{26}ClNO_3$: C, 70.92; H, 6.19; N, 3.30.

Found: C, 70.60; H, 6.31; N, 3.22.

The above hydrochloride (0.5 g.) was shaken under nitrogen with aqueous sodium carbonate (50 cc., 10%) until the crystalline material became amorphous and then was ex-

tracted with ether (50 cc., peroxide-free). The extract was dried, evaporated to 20 cc. under reduced pressure at room temperature, diluted with petroleum ether (10 cc.), and set aside at -15° . After a day the product (0.15 g., m.p., $96-99^{\circ}$) was crystallized from a mixture of ethanol and ether, when it melted at $104-106^{\circ}$. Both the amino ketone and its hydrochloride were unstable at room temperature, but were stable at 0° . The analytical sample of the amino ketone was dried at 0° under reduced pressure for two days.

Anal. Calc'd for $C_{25}H_{25}NO_3$: C, 77.52; H, 6.51; N, 3.62.

Found: C, 77.36; H, 6.40; N, 3.84.

SUMMARY

1. The preparation of the three phenyltrioses has been described, and these substances have been characterized.

2. The rearrangement of these substances, in dilute acetic acid, with and without the inclusion of amines, has been studied. The phenylaldotriose was converted into benzylglyoxal, but only in the presence of a primary, aromatic amine. The phenylketotrioses were converted into acetylbenzoyl, and the presence of an amine was not required for this transformation to occur.

3. A mechanism has been suggested to account for these reactions.

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REFERENCES

- (1) KUHN AND BIRKHOFFER, *Ber.*, **71**, 621 (1938).
- (2) PIGMAN AND GOEPP, *Carbohydrate Chemistry*, Academic Press, Inc., New York, 1948, pp. 375-426.
- (3) MITTS AND HIXON, *J. Am. Chem. Soc.*, **66**, 483 (1944).
- (4) WOLFROM, SCHUETZ, AND CAVALIERI, *J. Am. Chem. Soc.*, **71**, 3518 (1949).
- (5) WEYGAND, *Ber.*, **73**, 1259 (1940).
- (6) STRAIN AND SPOEHR, *J. Biol. Chem.*, **89**, 527 (1930).
- (7) HURD AND ISENHOUR, *J. Am. Chem. Soc.*, **54**, 317 (1932).
- (8) CAMERON, *Trans. Roy. Soc. Can.*, [3] **23**, Sect. III, 53 (1929); [3] **25**, Sect. III, 145 (1931).
- (9) COWPER AND STEVENS, *J. Chem. Soc.*, 347 (1940).
- (10) LUTZ, FREEK, AND MURPHEY, *J. Am. Chem. Soc.*, **70**, 2015 (1948); LUTZ AND MURPHEY, *J. Am. Chem. Soc.*, **71**, 478 (1949).
- (11) CLAISEN, *Ber.*, **40**, 3906 (1907).
- (12) FISCHER AND HOFFA, *Ber.*, **31**, 1995 (1898).
- (13) EVANS AND HASS, *J. Am. Chem. Soc.*, **48**, 2711 (1926).
- (14) RÜBER, *Ber.*, **48**, 827 (1915).
- (15) DAKIN, *J. Biol. Chem.*, **18**, 42 (1914).
- (16) FIESER, *Experiments in Organic Chemistry*, Second edition, D. C. Heath and Co., New York, 1941, p. 369.
- (17) HALE AND BRITTON, *J. Am. Chem. Soc.*, **41**, 844 (1919).
- (18) ALLEN, *J. Am. Chem. Soc.*, **62**, 661 (1940).
- (19) HARTMAN AND ROLL, *Org. Syntheses*, **23**, 1 (1943).
- (20) THAYER, *Org. Syntheses*, Coll. Vol. I, 12 (1941).
- (21) ARNDT, *Org. Syntheses*, Coll. Vol. II, 165 (1943).
- (22) WOLFROM AND COOPER, *J. Am. Chem. Soc.*, **72**, 1345 (1950).
- (23) FISCHER, *Ber.*, **34**, 433 (1901).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE STRUCTURE OF DIMERIC 3-C-PHENYLGLYCERALDEHYDE AND ITS REACTIONS WITH AMINES

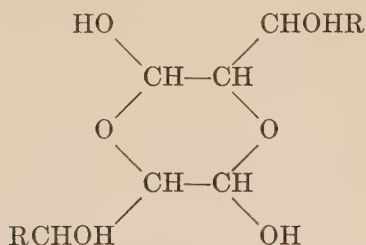
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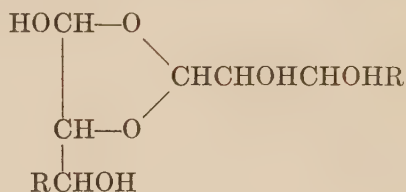
Under certain circumstances, glyceraldehyde exists as a dimer (1). It has been reported (2) that the dimer persists in solutions of glyceraldehyde in organic solvents, although the monomeric form exists in aqueous solutions.

It has now been found that β -phenylglyceraldehyde exhibits an analogous behavior. In aqueous solution, this triose exists in the monomeric form, but in organic solvents the triose exists as a dimer. The reactions of the monomer with amines have been discussed in the previous paper (3); the present paper constitutes a report of the reactions of the dimer in organic solvents.

Structure I ($R = H$) has been proposed (1) for the dimer of glyceraldehyde, but structures II and III ($R = H$) may also reasonably represent this substance. The three analogous structures (I, II, III, $R = C_6H_5$)

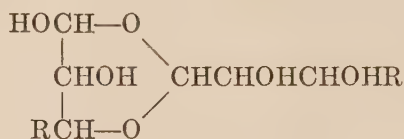


I. $R = H \text{ or } C_6H_5$



II. $R = H \text{ or } C_6H_5$.

V. $R = C_6H_5$; OH replaced by $-NHC_6H_5$.

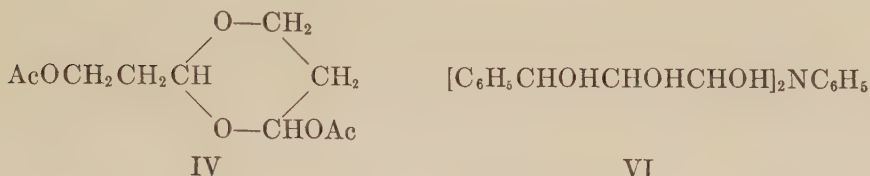


III. $R = H \text{ or } C_6H_5$

may likewise represent dimeric β -phenylglyceraldehyde.

Hall and Stern (4) showed that the diacetate (IV) of the dimer of β -hydroxypropionaldehyde underwent hydrolysis in two well-defined steps: one acetyl group was removed within five minutes by action of dilute (0.05 *N*) hydrochloric acid at 70°, whereas the second acetyl group was not entirely removed after two hours. This showed that the two acetyl groups in IV were situated differently within the molecule and lent considerable support to structure IV.

¹ Abstracted from a thesis by Ray H. Anderson, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1950.



Acetylation of dimeric β -phenylglyceraldehyde produced a crystalline tetraacetate, as required by structures I, II, and III. Depending upon the structure of the dimer, this tetraacetate would possess two different pairs of acetyl groups (I) or three acetyl groups alike, and one different (II, III). However, the rate of hydrolysis of the tetraacetate by action of dilute (0.05 *N*) hydrochloric acid at 70° showed no variation from the beginning to the end of the hydrolysis. It is not possible to write a structure for a dimer of β -phenylglyceraldehyde which contains four equivalent hydroxyl groups, so no choice as to the structure I, II, or III can be made on the basis of these results.

Reaction of the dimer with aniline in dioxane at room temperature resulted in a product (V) which separated in crystalline form when petroleum ether was added to the solution. The composition of V was that required by direct combination of one molecule of the dimer with one of aniline. The same substance V resulted when other conditions were used—other solvents (ethanol, etc.), temperatures varying from 20° to 85°, and excess aniline. The substance was unstable in water solution, and was very sensitive toward acids. It reduced Fehling's solution and an alkaline solution of methylene blue. The substance was not a Schiff base, nor was any carbonyl group present, for it was unaffected by action of hydrogen in the presence of a platinum catalyst. When V was subjected to prolonged drying under reduced pressure, slightly less than one molecule of water was evolved, and the composition agreed well with that required for a phenylglycosylamine. It has been reported several times (5) that crystalline glycosylamines usually contain water of crystallization which is held tenaciously. The properties of V therefore indicate that the substance is a phenylglycosylamine.

Since only one molecule of aniline is involved in the formation of V, it would appear that structures analogous to II and III, with the glycosidic hydroxyl group replaced by $\text{C}_6\text{H}_5\text{NH}$, would be most logical for V, and this, in turn, would indicate that dimeric β -phenylglyceraldehyde is best represented by II or III. The glycosylamine V cannot possess structure VI for this substance (V in the previous paper, 3) melts at 68° whereas V melts at 105°, and V (anhydrous) has the composition $\text{C}_{24}\text{H}_{25}\text{NO}_5$ as compared with $\text{C}_{24}\text{H}_{27}\text{NO}_6$ required for VI. Moreover, VI cannot be an intermediate in the formation of V, for VI decomposes under the conditions which lead to formation of V from aniline and dimeric β -phenylglyceraldehyde. No attempt was made to investigate the action of periodic acid upon V in view of the reports in the literature (6) that action of this reagent upon glycosylamines derived from sugars and primary aromatic amines, purines, or pyrimidines results in excessive consumption of periodic acid and leads only to tarry products.

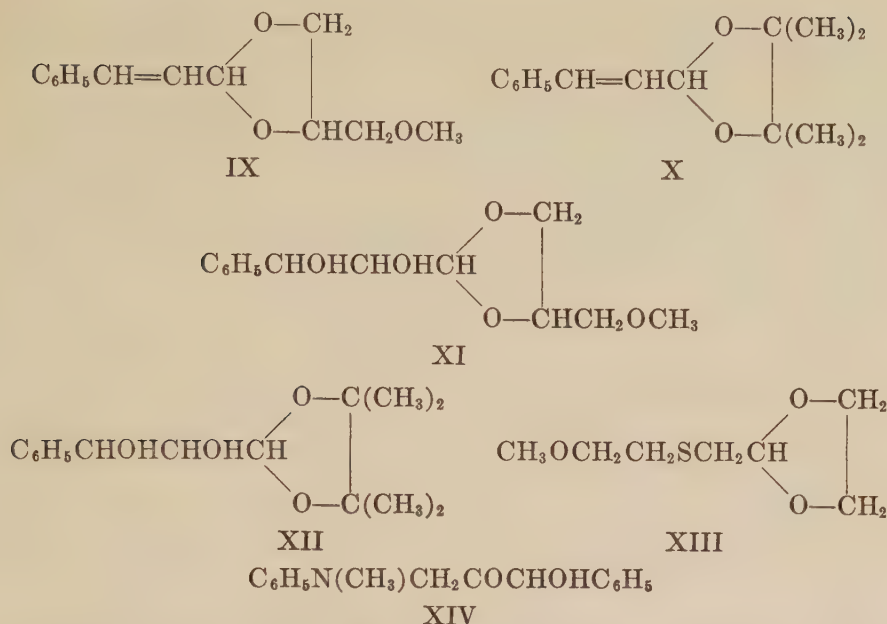
Acetylation of V by action of acetic anhydride in pyridine led to a tetraacetate VII. Measurement of the rate of hydrolysis of VII by action of dilute (0.05 *N*) hydrochloric acid at 70° indicated that three of the acetyl groups were removed at approximately the same rate—70 minutes for each acetyl group. No more acetic acid was produced by continuing the hydrolysis for two hours longer. This behavior indicates that of the four acetyl groups present in VII, three are structurally similar whereas one is different, and is in agreement with a structure for V related to II and III, but not to I. However, no acetanilide could be isolated from the tarry products of this hydrolysis.

Neither methyl iodide nor methyl sulfate could be used for alkylation of V, because V decomposed in solutions of these materials in dioxane at room temperature. A solution of V and methyl *p*-toluenesulfonate in benzene deposited a crystalline material (VIII) on standing at room temperature. This product, after crystallization from benzene, melted at 90°; it appeared to be a tetramethyl derivative of V, although the analytical value for hydrogen was somewhat low. Hydrolysis of VIII by the action of boiling aqueous sulfuric acid (15%) for six hours led to a brown solution from which neither methylaniline nor aniline could be isolated. Action of warm ethyl iodide upon V led to a solid melting at 127°. The analytical values for this material did not agree with any simple ethyl derivative of V nor could any ethylaniline be obtained from it by hydrolysis.

Dimeric β -phenylglyceraldehyde reacted with the ethyl ester of phenylalanine in dioxane at room temperature to give a crystalline material melting at 61–62°. The composition of this material indicated that it was derived from one molecule each of the dimer and the amine ester. It was thus analogous to V; the material appeared to be hydrated, but it was impossible to obtain it in anhydrous form for it was unstable above 30°. The substance was unstable in water, reduced Fehling's solution and an alkaline solution of methylene blue, and was very sensitive toward acids. It was recovered essentially unchanged when subjected, for six hours, to the action of hydrogen under 50 lbs. pressure at room temperature in the presence of a platinum catalyst.

The infrared absorption spectra of several compounds having a dioxolane ring were examined and compared with those of dimeric β -phenylglyceraldehyde and of V.² Cinnamaldehyde was converted into the cyclic acetals (dioxolanes) IX and X by reaction with the α -methyl ether of glycerol and pinacol, respectively. These unsaturated acetals were then hydroxylated using the method of Rüber (7), resulting in the hydroxy compounds XI and XII. The infrared absorption spectra of IX and XII, V, and the dimeric aldehyde were examined. The infrared spectra of the dimer, V, and XII showed a strong absorption, characteristic of hydroxyl groups, and which, in V, masked the characteristic frequencies of the amino group. None of the spectra showed any absorption characteristic of the carbonyl group.

² We wish to thank Dr. B. L. Crawford, Jr., and Mr. J. E. Lancaster of this laboratory for their kindness in measuring and interpreting the infrared spectra of these compounds. The complete curves are included in the Ph.D. thesis of R. H. Anderson, University of Minnesota, 1950.



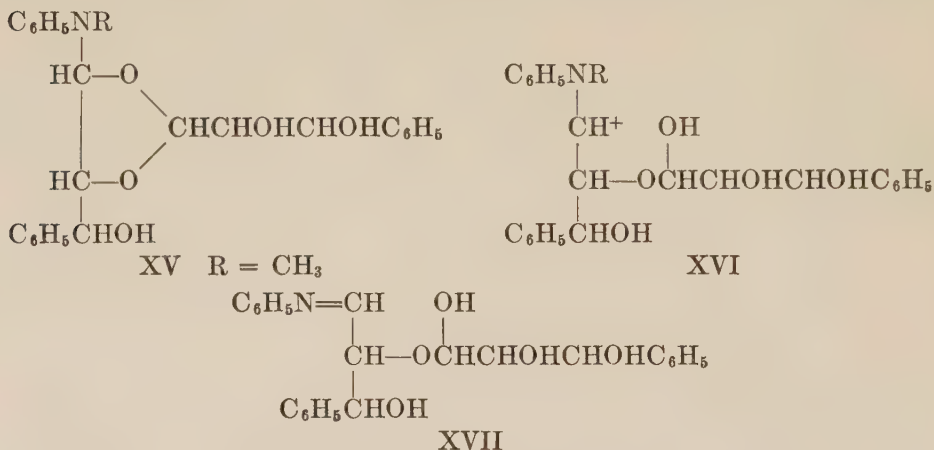
Comparison of these spectra with the spectrum of XIII (8) showed that all, except that of the dimer, possessed a strong adsorption band at 9.6μ in common with the spectrum of XIII. The data in the literature (9) do not include any group, common to all the compounds examined in this work, which has an absorption band at 9.6μ . It is therefore likely that the presence of a peak at 9.6μ in the spectrum of V indicates the presence of a dioxolane ring in V and hence the best structure for V is II with the glycosidic hydroxyl group replaced by $-\text{NHC}_6\text{H}_5$. The spectrum of the dimer of β -phenylglyceraldehyde showed a strong absorption band at 9.65μ indicating a dioxolane ring, but absorption is also strong at 9.55μ , and the latter is the position of an absorption band of dioxane. Hence, a definite choice among structures I and II for the dimer cannot be made.

Hydrolysis of XI produced a crystalline material identical in melting point and analysis with dimeric β -phenylglyceraldehyde. Hydrolysis of XII was so difficult that any conditions severe enough to bring about hydrolysis also brought about complete decomposition of the resulting triose.

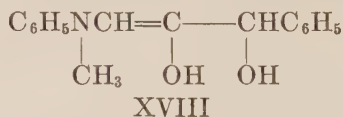
A solution of dimeric β -phenylglyceraldehyde in dioxane did not react with methylaniline during 24 hours at room temperature. But a solution of the dimer and methylaniline in ethanol containing acetic acid, refluxed for 30 minutes and then cooled, deposited a crystalline solid. This material, after crystallization from ethanol, melted at $103-104^\circ$. The substance was soluble in ether, alcohol, and dioxane and was only slightly soluble in water. It rapidly reduced Fehling's solution or a cold alkaline solution of methylene blue. Analytical values of the substance agreed well with those required by an aminoketol of structure XIV (or of the isomer with the carbonyl and hydroxyl groups

interchanged); in agreement with such a structure, the substance formed a white hydrochloride melting at 117–119°, and a pale yellow semicarbazone melting at 145–146°.

In the preceding paper (3) it was shown that action of aniline and other primary aromatic amines upon monomeric β -phenylglyceraldehyde led to benzylglyoxal; action of methylaniline did not bring about this transformation. The ketol XIV, therefore, must have been derived from dimeric β -phenylglyceraldehyde, and most likely by way of the glycosylamine, XV.



The question then arises as to why and how this glycosylamine XV is transformed into the ketol XIV, whereas the analogous product V (XV, R = H) derived from aniline, is not transformed into an analog of XIV. The salient differences between the two glycosides lie in the presence of a hydrogen atom on the nitrogen atom of one, and not the other, and in the basicity of the nitrogen atom itself. Both glycosides can give rise to a cation XVI; when R = H, this cation may change to the Schiff base XVII. When R = CH₃ a Schiff base cannot form; instead, a proton may be expelled from the adjacent carbon atom, leading eventually to XVIII and then to XIV. The Schiff base XVII, on the other hand, may decompose in some other manner, either directly or by reversion to XV (R = H) which is itself very sensitive toward acids.



EXPERIMENTAL PART³

Dimeric β -phenylglyceraldehyde. The aldehyde (0.1 g.) prepared as described in the previous paper (3), was dissolved in dioxane (10 cc.), and the molecular weight was determined by Rast's (10) modification of the method of Barger (11), using pinacol as the reference compound.

³ Microanalyses by R. W. Amidon, Jay S. Buckley, William Cummings, R. E. Kelly, and H. W. Turner.

Anal. Calc'd for $C_{18}H_{20}O_6$: M. W., 322. Found: M. W., 325, 316.

Tetraacetate (VII). The aldehyde (0.5 g.) was dissolved in anhydrous pyridine (2 cc.), acetic anhydride (2 cc.) was added, and the solution was boiled for three minutes. The cooled solution was poured into water (50 cc.), the solid was removed, washed successively with hydrochloric acid (2%) and water, and crystallized from ethanol. The acetate weighed 0.69 (60%) and melted at 89–91°.

Anal. Calc'd for $C_{26}H_{28}O_{10}$: C, 62.40; H, 5.64.

Found: C, 62.60; H, 6.00.

Hydrolysis. The tetraacetate (0.1206 g.) was mixed with hydrochloric acid (100 cc., 0.05 N) and the resulting solution was kept at 70°. At periodic intervals, 5-cc. aliquots were removed and titrated with aqueous sodium hydroxide (0.01 N) using phenolphthalein as the indicator. There was no preferential hydrolysis which would differentiate among the acetyl groups.

Reaction of the dimer with aniline: Product V. A solution of the aldehyde dimer (0.5 g.), and aniline (0.3 g.) in dioxane (10 cc.) was heated on the steam-bath for 20 minutes, cooled, and diluted with petroleum ether. The yellow solution, after a day at 15°, deposited 0.22 g. (36%) of solid which was crystallized from a mixture of dioxane and petroleum ether. The product, dried under reduced pressure at room temperature, melted at 102–104°. It was stable at 0°, but became yellow after standing for two weeks at room temperature. The instability was increased markedly by traces of the yellow impurity.

Anal. Calc'd for $C_{24}H_{25}NO_5$: C, 70.76; H, 6.19; N, 3.44.

Calc'd for $C_{24}H_{25}NO_5 \cdot H_2O$: C, 67.78; H, 6.35; N, 3.3.

Found: C, 68.16; H, 6.53; N, 3.22.

The experiment was duplicated, but the solution was not heated; instead, it was allowed to stand for four hours at room temperature. Petroleum ether was then added and the mixture was processed as above. The crystalline material weighed 0.37 g. (60%) and melted, after crystallization, at 101–105°. If the solution was allowed to stand for longer than four hours, it became progressively more yellow, and it was difficult to isolate the solid from it.

Anal. Found: C, 68.19; H, 6.56; N, 3.12.

The product from experiment 2 was dried for eight hours under reduced pressure at 65°; it then melted at 103–104°.

Anal. Found: C, 69.67; H, 6.62; N, 3.51.

The experiment was duplicated except that ethanol was used in place of dioxane. The mixture was refluxed for 20 minutes and then set aside at –15°, no petroleum ether being added. The solid (0.12 g., 20%) was recrystallized from ethanol and dried at 65° for eight hours under reduced pressure; m.p. 104–106°.

Anal. Calc'd for $C_{24}H_{25}NO_5$: C, 70.76; H, 6.19; N, 3.44.

Found: C, 70.43; H, 6.24; N, 3.61.

Each of the products obtained from the above experiments reduced Fehling's solution and alkaline methylene blue at room temperature. The material (0.3 g.) from the second experiment was dissolved in dioxane (10 cc.) and the solution was subjected to the action of hydrogen under 50 lb. pressure for six hours at room temperature in the presence of a platinum catalyst. The catalyst was removed and the product was isolated as above and crystallized from a mixture of dioxane and petroleum ether. It was then dried at 65° for eight hours under reduced pressure, when it melted at 99–102°. It reduced Fehling's solution, and was unchanged V.

Anal. Found: C, 69.39; H, 6.68; N, 3.62.

Substance V (0.1 g.) was dissolved in dioxane (10 cc.) and the molecular weight was determined by the Rast-Barger method (10, 11) using pinacol as the reference compound.

Anal. Calc'd for $C_{24}H_{25}NO_5$: M. W., 407. Found: M. W., 425, 414.

Tetraacetate VII. Substance V (0.5 g.) was dissolved in dry pyridine (5 cc.), acetic anhydride (2 cc.) was added, and the solution was allowed to stand overnight at room temperature. It was poured into ice-water (50 cc.), and the amorphous product was removed

by ether extraction. The extract was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, and was dried and concentrated to a volume of 5 cc. Petroleum ether (2 cc.) was added and the solution was set aside at -15° . After a day, the solid was removed and crystallized from a mixture of petroleum ether and ether, when it weighed 0.37 g. (53%) and melted at $136-138^{\circ}$.

Anal. Calc'd for $C_{32}H_{33}NO_3$: C, 66.78; H, 5.78; N, 2.43.

Found (dried 8 hrs. at 74° under reduced pressure): C, 66.15; H, 6.30.

Found (dried 24 hours at 74° under reduced pressure): C, 66.30; H, 6.15; N, 2.36.

The analytical sample decomposed when it was dried for four hours at 100° under reduced pressure.

Hydrolysis. The tetraacetate VII (0.1387 g.) was mixed with hydrochloric acid (100 cc., 0.05 *N*) and the solution was kept at 70° . Aliquots of 5 cc. were removed at periodic intervals and titrated with aqueous sodium hydroxide (0.01 *N*) using phenolphthalein. The data showed that three acetyl groups were removed in regular sequence, 70 minutes for each, but that no further removal of acetyl groups occurred during an additional $2\frac{1}{2}$ hours. No acetanilide separated from the solution during the hydrolysis, nor from the cooled solution remaining after hydrolysis.

Tetramethyl derivative (VIII) of V. A solution of V (0.5 g.) and methyl *p*-toluenesulfonate (1 g.) in benzene (30 cc.) was allowed to stand overnight at room temperature. The solid was crystallized, first from benzene, and then from aqueous ethanol, when it weighed 0.4 g. and melted at 90° .

Anal. Calc'd for $C_{28}H_{33}NO_6$ (tetramethyl): C, 72.33; H, 7.17; N, 3.05.

Found: C, 72.64; H, 6.53; N, 2.97.

This material was refluxed for six hours with aqueous sulfuric acid (15%). The brown solution was extracted with ether; the aqueous layer was neutralized with sodium bicarbonate and again extracted with ether. The solvent was evaporated from the second ether extract and the residual oil was subjected to the action of acetic anhydride and alkali. No *N*-methylacetanilide could be isolated from the tarry product.

Ethylation of V. No reaction occurred when V (0.3 g.) and ethyl iodide (0.3 g.) were dissolved in dioxane (2 cc.) and the solution was allowed to stand at room temperature for a day. Unchanged V was recovered. But when V (0.5 g.) was warmed with ethyl iodide (5 cc.), solution occurred and then a solid was quickly deposited. This solid began to decompose to a brown oil after about ten minutes in the refluxing ethyl iodide, so the experiment was interrupted, and the solid was removed and washed thoroughly with ether. The product obtained in this way weighed 0.45 g. and melted at 127° .

Anal. Calc'd for $C_{26}H_{29}NO_5$ (monoethyl): C, 71.72; H, 6.68; N, 3.22.

Found: C, 69.91; H, 6.23; N, 3.55.

After crystallization from aqueous ethanol, the substance melted at 124° and was evidently undergoing decomposition.

Anal. Found: C, 69.34; H, 6.54; N, 3.45.

The analytical values of this substance agree well with those required by V from which it was derived, yet the melting points of the two substances are quite different. Action of sulfuric acid (15%) upon this product led only to a brown tar; no ethylaniline could be isolated from the product.

2-Styryl-4-methoxymethyl-1,3-dioxolane (IX). In agreement with Hibbert and Whelen (12), it was found that reaction between cinnamaldehyde and a glycol led to very small yields of cyclic acetals. But by modifying the procedure of Hibbert and Whelen, a good yield of IX was obtained. Cinnamaldehyde (13 g.) and glycerol- α -methyl ether (12 g.) were dissolved in benzene (100 cc.), *p*-toluenesulfonic acid (0.5 g.) was added, and the mixture was refluxed in an apparatus which included a water trap. After the calculated amount of water (1.8 cc.) had collected in the trap (one hour), the solution was washed with aqueous sodium bicarbonate, dried, and the solvent was removed. The residual liquid was distilled at 6 mm., and the fraction boiling at 155° was collected. This weighed 21 g. (90%); n_D^{25} 1.5440, as reported by Hibbert and Whelen (12).

2-(β -Phenyl- α,β -dihydroxyethyl)-4-methoxymethyl-1,3-dioxolane (XI). The unsaturated

dioxolane (IX) (13.5 g.) was dissolved in ethanol (750 cc.) and hydroxylated at -40° according to Rüber (7) by the slow addition of a solution of potassium permanganate (12 g.) in water (400 cc.). The mixture was allowed to come to room temperature, and the brown manganese dioxide was removed. The filtrate was concentrated to a volume of 100 cc. and extracted with four 50-cc. portions of ether. The combined extracts were dried, concentrated to a volume of 25 cc., diluted with petroleum ether, and cooled to -15° . The product separated as an oil which could not be crystallized. The oil was distilled to give XI (1.5 g.), b.p. $190^{\circ}/0.7$ mm.

The acetal XI (0.5 g.) was stirred with dilute sulfuric acid (5 cc., 1%) at 60° for three hours and the solution was kept overnight at room temperature. The crystalline material was removed; it reduced Tollens' solution, melted at $123-125^{\circ}$, and was β -phenylglyceraldehyde, although the analytical values for carbon were low, as is always the case for this compound.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.06; H, 6.03.

Found: C, 62.96; H, 6.40.

2-Styryl-4,4,5,5-tetramethyl-1,3-dioxolane (X). Cinnamaldehyde (13 g.) and pinacol (13 g.) were dissolved in benzene (100 cc.), *p*-toluenesulfonic acid (0.5 g.) was added, and the reaction was conducted as described for the preparation of IX above. The product was a colorless liquid (22 g., 90%), b.p. $142^{\circ}/4$ mm. and n_D^{25} 1.5265.

Anal. Calc'd for $C_{15}H_{20}O_2$: C, 77.58; H, 8.68.

Found: C, 77.34; H, 8.81.

2-(β -Phenyl- α,β -dihydroxyethyl)-4,4,5,5-tetramethyl-1,3-dioxolane (XII). The unsaturated dioxolane X (13.5 g.) was hydroxylated as described above for the preparation of XI. The product, crystallized from aqueous ethanol, weighed 6 g. (37%) and melted at 120° .

Anal. Calc'd for $C_{15}H_{22}O_4$: C, 67.67; H, 8.34.

Found: C, 67.78; H, 8.45.

The acetal XII (1 g.) in dioxane (10 cc.) was heated to 60° and stirred for four hours with aqueous sulfuric acid (8 cc., 2%). No hydrolysis of XII occurred; the cooled solution deposited unchanged XII, m.p., 120° .

3-Phenylmethylamino-1 (or 2)-hydroxy-1-phenyl-2 (or-1)-propanone (XIV). β -Phenylglyceraldehyde (0.5 g.) and methylaniline (0.4 g.) were dissolved in dioxane (10 cc.) and the solution was allowed to stand at room temperature for one day. Petroleum ether was added, and the pale yellow solution was set aside at -15° for one day. The crystalline solid was unchanged aldehyde but was impure. It melted at $101-103^{\circ}$, and contained no nitrogen.

β -Phenylglyceraldehyde (0.5 g.) and methylaniline (0.4 g.) were dissolved in dry ethanol (10 cc.) containing acetic acid (0.5 cc.). The solution was refluxed for 30 minutes, then cooled, diluted with water, and set aside at -15° . The white crystalline material (0.3 g., 45%) was crystallized from dry ethanol, m.p. $103-104^{\circ}$. The amino ketone reduced Fehling's solution and alkaline methylene blue at room temperature.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.28; H, 6.72; N, 5.50.

Found: C, 75.20; H, 6.87; N, 5.36.

Hydrochloride. Addition of hydrogen chloride to an ethereal solution of XIV resulted in precipitation of the white hydrochloride. It melted at $117-119^{\circ}$, and was only slightly soluble in cold water.

Anal. Calc'd for $C_{16}H_{18}ClNO_2$: C, 66.00; H, 6.23; N, 4.81.

Found: C, 65.82; H, 6.39; N, 4.71.

Semicarbazone. A solution of XIV (0.3 g.) in ethanol (5 cc.) was added to an aqueous solution of semicarbazide hydrochloride and potassium acetate, and the mixture was warmed for two minutes on the steam-bath. The pale yellow semicarbazone separated when the solution was cooled. It was recrystallized from ethanol, m.p. $145-146^{\circ}$.

Anal. Calc'd for $C_{17}H_{20}N_4O_2$: C, 65.38; H, 6.46; N, 17.95.

Found: C, 65.46; H, 6.70; N, 17.67.

Reaction of dimeric β -phenylglyceraldehyde with phenylalanine ester. The aldehyde

(0.7 g.) and phenylalanine ester (0.87 g.) were dissolved in dioxane (10 cc.) and the solution was allowed to stand at room temperature for six hours under nitrogen. Dioxane was removed at 0° under reduced pressure until the volume of the solution was about 2 cc. This residue, set aside at 0° for one day, solidified. The dioxane was allowed to melt, and the remaining solid was removed and crystallized from a mixture of dioxane and petroleum ether. The material weighed 0.52 g. (46%), m.p. 61–62°. It reduced Fehling's solution and alkaline methylene blue, and was very unstable at room temperature—standing for longer periods than about one hour at room temperature, even under reduced pressure, resulted in decomposition and the resulting yellow impurity, if present even in traces, greatly accelerated the decomposition.

Anal. Calc'd for $C_{20}H_{23}NO_7$: C, 68.64; H, 6.56; N, 2.76.

Found: C, 67.20; H, 6.97; N, 2.39.

The experiment was duplicated except that the solution of the reagents, after standing for six hours at room temperature, was diluted with petroleum ether (40 cc.) and then cooled to –15°. The product in this case was an oil from which no crystalline material could be obtained.

The solid product (0.4 g.) in dioxane (20 cc.) was subjected for six hours to the action of hydrogen under 50 lb. pressure at room temperature in the presence of a platinum catalyst. The catalyst was removed, the filtrate was concentrated at 0° under reduced pressure to a volume of 4 cc., diluted with petroleum ether (10 cc.), and set aside at –15°. The solid was removed and crystallized from a mixture of dioxane and petroleum ether, when it melted at 56–59° and was identical with the starting material. No reduction occurred.

Anal. Found: C, 66.92; H, 7.53; N, 2.31.

SUMMARY

1. β -Phenyglyceraldehyde has been found to exist in a dimeric form in organic solvents. The structure of the dimer has been investigated; three structures have been considered, and some evidence has been obtained favoring structure II for the dimer.

2. Aniline, as well as phenylalanine ethyl ester, react with the dimer in organic solvents, giving crystalline products to which structures have been assigned.

3. Reaction of the dimer with methylaniline in organic solvents produces a crystalline aminoketol, XIV.

MINNEAPOLIS 14, MINNESOTA

REFERENCES

- (1) WOHL AND NEUBERG, *Ber.*, **33**, 3095 (1900).
- (2) FISCHER, *Ber.*, **60**, 479 (1927).
- (3) SMITH AND ANDERSON, *J. Org. Chem.*, preceding article.
- (4) HALL AND STERN, *J. Chem. Soc.*, 490 (1950).
- (5) IRVINE AND GILMOUR, *J. Chem. Soc.*, **93**, 1429 (1908); KARRER AND SALOMON, *Helv. Chim. Acta*, **20**, 1016 (1937); MITTS AND HIXON, *J. Am. Chem. Soc.*, **66**, 483 (1944).
- (6) KENNER, RODDA, AND TODD, *J. Chem. Soc.*, 1613 (1949); BERGER AND LEE, *J. Org. Chem.*, **11**, 75 (1946).
- (7) RUBER, *Ber.*, **48**, 827 (1915).
- (8) ZUCKERBRAUN, M.S. Thesis, University of Minnesota, 1948.
- (9) RANDALL, FOWLER, FUSON, AND DANGL, *Infra Red Determinations of Organic Structures*, D. Van Nostrand and Co., New York, 1949.
- (10) RAST, *Ber.*, **54**, 1979 (1921).
- (11) BARGER, *Ber.*, **37**, 1754 (1904); *J. Chem. Soc.*, **85**, 286 (1904).
- (12) HIBBERT AND WHELEN, *J. Am. Chem. Soc.*, **51**, 620 (1929).

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